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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

# (54) Substituted Acetamide Compound

(72) Shiokawa, Youichi - Japan ;
Taniguchi, Kiyoshi - Japan ;
Take, Kazuhiko - Japan ;
Tsubaki, Kazunori - Japan ;
Mizuno, Hiroaki - Japan ;

(71) Fujisawa Pharmaceutical Co., Ltd. - Japan ;

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SPECIFICATION

Title of the Invention

# SUBSTITUTED ACETAMIDE COMPOUND

Field of the Invention

This invention relates to a novel substituted acetamide compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to a novel substituted-acetamide compound and a pharmaceutically acceptable salt thereof which have anticholinergic activity, and are useful for the treatment of dysuria such as pollakiuria, urinary incontinence or the like in case of nervous pollakiuria, neurogenic bladder dysfuction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis or the like; and for the treatment of convulsion and/or hypanakinesis in case of gastric ulcer, duodenal ulcer, gastroxynsis, esophagospasm, gastritis, enteritis, irritable colon syndrome, enteralgia, cholecystitis, cholangitis, pylorospasm, pancreatitis, pain in case of pancreatitis, biliary dyskinesia, aftereffect after cholecystectomy, urinary calculus cystitis, dysmenorrhea, hidrosis, convulsion of urinary tract; and which are expected to be useful for the treatment of asthma, Parkinson disease, angina pectris or the like.

Prior Art

One object of this invention is to provide a novel substituted acetamide compound and a pharmaceutically acceptable salt thereof which are useful for the treatment of aforesaid diseases.

Another object of this invention is to provide a pharmaceutical preparation comprising, as an active ingredient, said substituted acetamide compound or a pharmaceutically acceptable salt thereof, which is useful as an agent for the treatment of aforesaid diseases.

Disclosure of the Invention

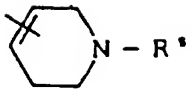
The object substituted acetamide compound of this invention is novel and can be represented by the following formula (I):

$$R^1-\underset{\displaystyle R^3}{\overset{\displaystyle R^2}{\overset{|}{\underset{|}{C}}}}-(A^1)_a-CONH-(A^2)_b-R^4 \qquad (I)$$

wherein $R^1$ and $R^2$ are each aryl which may have suitable substituent,

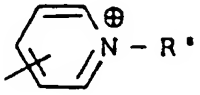
$R^3$ is hydrogen, hydroxy or lower alkyl,

$R^4$ is a group represented by the following formula (i), (ii), (iii) and (iv):



(I)

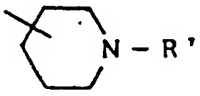
wherein $R^5$ is hydrogen, methyl, ethyl, propyl, isopropyl or imino protective group,



(II)

wherein $R^6$ is lower alkyl,

(III)



(IV)

wherein $R^7$ is hydrogen, lower alkyl or imino protective group,

$A^1$ and $A^2$ are each lower alkylene, and

m and n are each 0 or 1,

provided that

(a) $R^5$ is not ethyl when $R^1$ and $R^2$ are both phenyl,

$R^3$ is hydroxy, $A^2$ is methylene, m is 0 and n is 1,

(b) $R^7$ is not methyl when $R^1$ and $R^2$ are both phenyl, $R^3$ is hydroxy, and m and n are both 0.

The object compound (I) may have (an) asymmetric carbon atom(s) and the stereo isomer caused by asymmetry is also included in the scope of the present invention.

For the preparation of the object compound (I), a starting compound which may be prepared according to the "Preparation" exemplarily illustrated later may be reacted according to the "Example" also exemplarily illustrated later.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic mono or di salts and include an organic acid addition salt [e.g., formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt [e.g., hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.], a salt with an amino acid [e.g., arginine salt, aspartic acid salt, glutamic acid salt, etc.], metal salt such as alkali metal salt [e.g., sodium salt, potassium salt, etc.], alkaline earth metal salt [e.g., calcium salt, magnesium salt, etc.], ammonium salt, a salt with an organic base [e.g., trimethyl amine salt, triethyl amine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzyl ethylenediamine salt, etc.], and the like.

In the above and subsequent descriptions of this specification, suitable of the various definitions are explained in

detail as follows:

The term "lower" is intended to mean 1 to 6 carbon atom(s), preferably to 1 to 4 carbon atom(s).

Suitable "aryl" in "aryl which may have suitable substituent" may include phenyl, naphthyl, pentalenyl, anthracenyl and the like.

"Suitable substituent" which may be substituted with the above "aryl" may include halogen (e.g., fluorine, chlorine, bromine, iodine), lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, etc.), and the like. A number of substituent substituted to aryl may be one or more than one, preferably one to three.

Accordingly, suitable "aryl which may have suitable substituent" may include phenyl which has one suitable substituent selected from the group consisting of halogen, lower alkyl and lower alkoxy, in which the preferred one may be phenyl which has halogen, phenyl which has $(C_1-C_4)$alkyl or phenyl which has $(C_1-C_4)$alkoxy, and the more preferred one may be phenyl which has chlorine, phenyl which has fluorine, phenyl which has methyl or phenyl which has methoxy.

Suitable "lower alkyl" may include the straight and branched ones such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl or the like, in which the preferred one may be $(C_1-C_4)$alkyl, and the more preferred one may be methyl.

ethyl, propyl, isopropyl, butyl or t-butyl.

Suitable "imino-protective group" may include the conventional protective group such as substituted or unsubstituted ar(lower)alkyl (e.g., trityl, benzhydryl, benzyl, 4-methoxybenzyl, etc.), dinitrophenyl, lower alkoxy carbonyl(lower)alkenyl (e.g., 1-methoxycarbonyl-1-propene-2-yl, etc.), aroyl(lower)alkenyl (e.g., 1-benzoyl-1-propene-2-yl, etc.), hydroxy ar(lower)alkylidine (e.g., 2-hydroxybenzylidene, etc.), silyl compound such as tri(lower)alkylsilyl (e.g., trimethyl silyl, etc.), acyl as exemplified as follows, and the like.

Suitable "acyl" may include aliphatic acyl group, aromatic acyl group, heterocyclic acyl group, and aliphatic acyl group wherein the aliphatic chain is substituted with aromatic group or heterocyclic group.

Suitable "aliphatic acyl group" may include saturated or unsaturated, acyclic or cyclic acyl such as carbamoyl, lower alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, varelyl, isovarelyl, pivaloyl, hexanoyl, etc.), lower alkane sulfonyl (e.g., mesyl, ethane sulfonyl, propane sulfonyl, etc.), lower alkoxy carbonyl (e.g., methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, butoxy carbonyl, tert-butoxy carbonyl, etc.), lower alkenoyl (e.g., acryloyl, methacryloyl, crotonoyl, etc.), ($C_3$-$C_7$)cycloalkane carbonyl (e.g., cyclohexane carbonyl, etc.), amidino, protected carboxy carbonyl such as lower alkoxalyl (e.g., methoxalyl, ethoxalyl, tert-butoxalyl, etc.), and the like.

Suitable "aromatic acyl group" may include aroyl (e.g., benzoyl, toluoyl, xyloyl, etc.), arene sulfonyl (e.g., benzene sulfonyl, tosyl, etc.), and the like.

Suitable "heterocyclic acyl group" may include heterocyclic carbonyl (e.g., furoyl, thenoyl, nicotinoyl isonicotinoyl, thiazolyl carbonyl, thiadiazolyl carbonyl, tetrazolyl carbonyl, morpholino carbonyl, etc.), and the like.

Suitable "aliphatic acyl group wherein the aliphatic chain is substituted with aromatic group" may include ar(lower)alkanoyl such as phenyl(lower)alkanoyl (e.g., phenyl acetyl, phenyl propionyl, phenyl hexanoyl, etc.), ar(lower)alkoxy carbonyl such as phenyl(lower)alkoxy carbonyl (e.g., benzyloxycarbonyl, phenetyloxy carbonyl, etc.), phenoxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.), and the like.

Suitable "aliphatic acyl group wherein the aliphatic chain substituted with heterocyclic group" may include thienyl acetyl, imidazolyl acetyl, furyl acetyl, tetrazolyl acetyl, thiazolyl acetyl, thiadiazolyl acetyl, thienyl propionyl, thiadiazolyl propionyl, and the like.

Above exemplified acyl may be further substituted with carboxy, lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl, etc.), halogen (e.g., chlorine, bromine, iodine, fluorine), carbamoyl, lower alkanoyl (e.g., formyl, acetyl, propionyl, etc.), ar(lower)alkyl (e.g., benzyl, etc.), lower alkyl (e.g., methyl, ethyl, propyl, isopropyl,

butyl, tert-butyl, etc.), lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), ar(lower)alkyloxycarbonyl (e.g., benzyloxycarbonyl, etc.), aryloxycarbonyl (e.g., phenyloxycarbonyl, etc.), carboxy(lower)alkyl (e.g., carboxymethyl, carboxyethyl, etc.), protected carboxy(lower)alkyl (e.g., tert-butoxycarbonylmethyl, etc.), or the like.

Suitable "lower alkylene" may include the straight and branced ones such as methylene, ethylene, trimethylene, tetramethylene, 1,1-dimethylethylene, pentamethylene, hexamethylene, or the like, in which the preferred one may be $(C_1-C_4)$alkylene, and the more preferred one may be methylene and ethylene. In the object compound (I), direct chemical bond is formed without a lower alkylene when m and/or n is 0.

Each definition of the present invention is as described above with representatives thereof. The object compound (I) is constructed under the optimum assortment of each difinition excepting the specific under-mentioned assortment.

(a) an assortment that both $R^1$ and $R^2$ are phenyl, $R^3$ is hydroxy, $A^2$ is methylene, m is 0, n is 1, and $R^5$ is ethyl

(b) an assortment that both of $R^1$ and $R^2$ are respectively phenyl, $R^3$ is hydroxy, m and n are respectively 0 and $R^7$ is methyl

Most preferred difinition of the present invention includes the following assortment, i.e., $R^1$ and $R^2$ are respectively phenyl or phenyl which has fluorine, $R^3$ is hydrogen, hydroxy or

methyl, m is 0 or 1, $A^1$ is methylene, n is 0 or 1, $A^2$ is methylene or ethylene, $R^5$ is hydrogen, methyl, ethyl, isopropyl, imino-protective group, $R^6$ is ethyl, $R^7$ is hygrogen, methyl, ethyl, isopropyl or imino-protective group.

Effect of the Invention

The object compound (I) and a pharmaceutically acceptable salt thereof of this invention have anticholinergic activity and are useful for the treatment of dysuria or other diseases as mentioned before in human being and animals.

In the object compound (I) and a pharmaceutically acceptable salt thereof, side effect such as mydriasis or the like is alleviated.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the representative compound of this invention is shown in the following.

Test 1

Test on Inhibition of Urinary Bladder Contractions Induced by Water Filing in Rats

[1] Test Method

Male Sprague-Dawly rats, weighing 240-450 g, were anesthetized with urethane 1.0 g/kg s.c. The bladder was exposed through a midline incision in the abdomen for the recording of pressure within the bladder as follows; a balloon attached to one

end of a stainless steel tube (O.D., 1.2 mm, 5 cm in length) was inserted into the bladder through a small incision in the bladder dome. The other end of the tube was connected to a pressure-transducer. The ureters were ligated and cut, and the proximal cut end was cannulated with polyethylene tubing and the urine was led outside.

Hyperactive urinary bladder (hyperactive contractions of the detrusor muscle) was induced by water filling of the bladder. Therefore, the balloon in the bladder was filled with water of a volume which caused a resting pressure of about 10 mmHg. Systemic blood pressure and heart rate were monitored from the common carotid artery.

When the contractile responses to water filling became constant, test compounds were administered intravenously.

[II] Test Compound

The Compound (I): N-(1,2,3,6-tetrahydropyridin-4-yl)methyl-2-hydroxy-2,2-diphenylacetamide

[III] Test Result

The $ED_{30}$ value (mg/kg) was as follows.

$ED_{30}$ = 0.005 (mg/kg)

The pharmaceutical composition of this invention (an agent for the prevention and/or the treatment of dysuria) can be used in the form of a pharmaceutical preparation, for example, in

solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation or intravesica administration. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carrier for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. And, if necessary, in addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The object compound (I) or a pharmaceutical acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For applying the composition to human being or animal, it is preferable to apply it by intravenous, intramuscular, pulmonary, or oral administration, or insufflation. While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 20 mg of the object compound (I) per kg weight of human being or animal, in the case of intramuscular administration, a daily dose of 0.1 - 20 mg of the

object compound (I) per kg weight of human being or animal, in case of oral administration, a daily dose of 0.5 - 50 mg of the object compound (I) per kg weight of human being or animal is generally given for treating or preventing the aforesaid diseases.

The following Preparations and Examples are given for the purpose of illustrating this invention in more detail.

Preparation 1

Benzilic acid (5.00 g) and phosphorus pentachloride (9.4 g) were stirred at 100 ℃ for 3.5 hours. After cooling, the reaction mixture was partitioned between ice-water (50 ml) and diethyl ether (100 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated to give crude 2-chloro-2,2-diphenylacetyl chloride (6.16 g). A solution of 4-(aminomethyl)pyridine (1.97 g) in dry toluene (5 ml) was added dropwise to a solution of crude 2-chloro-2,2-diphenylacetyl chloride (6.16 g) in dry toluene (50 ml) at room temperature. The reaction mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (50 ml) and 1N sodium hydroxide solution (50 ml). The organic layer was separated, washed with 1N-sodium hydroxide solution (50 ml x 3), and evaporated to give crude N-(pyridine-4-yl)methyl-2-chloro-2,2-diphenylacetamide (9.06 g). A solution of the crude N-(pyridine-4-yl)methyl-2-chloro-2,2-diphenylacetamide (9.06 g) in 1N hydrochloric acid

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(50 ml) was stirred at 70℃ for 2 hours. After cooling, the solution was washed with diethyl ether (50 ml) and was made alkaline with 6N sodium hydroxide solution. The precipitated powder was collected by filtration to give N-(pyridine-4-yl)methyl-2-hydroxy-2,2-diphenylacetamide (6.37 g) as a colorless powder.

mp : 148-151 ℃

IR(Nujo') : 3330, 1650, 1600, 760, 740, 690cm⁻¹

NMR(DMSO-d₆, δ) : 4.33(2H, d, J=6.3Hz), 6.85(1H, s),
7.15-7.18(2H, m), 7.25-7.40(10H, m), 8.42-8.45(2H, m),
8.84(1H, t, J=6.3Hz)

MASS(m/z) : 183, 105

Preparation 2

A solution of N-(pyridine-4-yl)methyl-2-hydroxy-2,2-diphenylacetamide (80 g) and 4-methoxybenzyl chloride (47.2 g) in N,N-dimethylformamide (120 ml) was stirred at 65 ℃ for 1 hour. After cooling, the reaction mixture was diluted with acetone (500 ml) and diethyl ether (100 ml) and stirred under ice cooling for 20 minutes. The precipitated powder was collected by filtration to give 4-[(2-hydroxy-2,2-diphenylacetylamino)methyl]-1-(4-methoxybenzyl)pyridinium chloride (107.57 g) as a colorless powder.

mp:205-208℃

IR(Nujol) : 3250, 3050, 1650, 1610, 750, 700cm⁻¹

NMR(DMSO-d₆, δ) : 3.76(3H, s), 4.55(2H, d, J=5.9Hz),
5.72(2H, s), 6.99(2H, d, J=6.7Hz), 7.00(1H, s),

7.25-7.40(10H. m). 7.53(2H. d. J=6.7Hz).

7.87(2H. d. J=6.7Hz). 9.13(2H. d. J=6.7Hz).

9.11(1H. t. J=5.9Hz)

MASS(m/z) : 183. 93

Preparation 3

A solution of 4-acetylaminomethylpyridine (7.00 g) and 4-methoxybenzyl chloride (6.8 ml) in acetone (100 ml) was stirred for 4 hours under reflux and then for 30 minutes under ice cooling. The precipitated powder was collected by filtration and washed with acetone to give hygroscopic 4-acetylamino-methyl-1-(4-methoxybenzyl)pyridinium chloride (10.88 g) which was used for next step reaction (Preparation 4) without further purification.

Preparation 4

To a solution of 4-acetylaminomethyl-1-(4-methoxybenzyl)pyridinium chloride (10.88 g) in methanol (200 ml) was added portionwise sodium borohydride (5.37 g) under ice cooling and the resulting solution was stirred at room temperature for 13 hours. Water (10 ml) was added to the reaction solution, and the solvent was distilled off. Ethyl acetate and water were added to the residue, and the organic layer was separated, washed with brine, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silicagel with an eluent of a mixture of methylene chlo-

ride and methanol (15:1) to give 4-acetylaminomethyl-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (7.27 g) as a pale yellow oil.

IR(film) : 3300, 1650, 1610, 760cm$^{-1}$

NMR(CDCl$_3$, $\delta$) : 1.98(s, 3H), 2.10(br s, 2H),
2.56(t, J=5.7Hz, 2H), 2.95(br s, 2H), 3.52(s, 2H),
3.76(s, 2H), 3.80(s, 3H), 5.53(t, J=1.5Hz, 1H),
5.95(br s, 1H), 6.80-6.90(m, 2H), 7.20-7.30(m, 2H)

MASS(m/z) : 274(M$^+$), 215, 121

Preparation 5

4-Acetylaminomethyl-1-propylpyridinium iodide was obtained by reacting 4-acetylmethylpyridine as a raw material, in a similar manner to that of Preparation 3.

mp : 135-137 ℃ (washed with acetone)

IR(Nujol) : 3250, 1670, 1640, 760, 750 cm$^{-1}$

NMR(DMSO-d$_6$, $\delta$) : 0.87(t, J=7.3Hz, 3H), 1.65-2.00(m, 2H),
1.97(s, 3H), 4.45-4.55(m, 4H), 7.96(d, J=6.8Hz, 2H)
8.67(t, J=5.8Hz, 1H), 8.98(d, J=6.8Hz, 2H)

MASS(m/z) : 193(M$^+$), 149, 107

Preparation 6

4-Acetylaminomethyl-1-propyl-1,2,3,6-tetrahydropyridine was obtained by reacting the compound obtained in Preparation 5 as a raw material, in a similar manner to that of Preparation 4.

IR(film) : 3300. 3050. 1650. 750cm

NMR($CDCl_3$, $\delta$) : 0.91(t. J=7.3Hz. 3H).

1.58(t. quartet. J=7.3Hz. J=5.7Hz. 2H). 1.99(s. 3H).

2.23(br s. 2H). 2.30-2.40(m. 2H). 2.56(t. J=5.7Hz. 2H)

2.95(d. J=1.6Hz. 2H). 3.79(d. J=5.4Hz. 2H).

5.54-5.57(m. 1H). 5.66(br s. 1H)

MASS(m/z) : 196($M^+$). 167. 96

Preparation 7

3-Acetylamino-1-ethyl-1,2,3,6-tetrahydropyridine was obtained as an oil by reacting 3-acetylaminomethyl-1-ethylpyridinium iodide as a raw material, in a similar manner to that of Preparation 4.

bp 150 ℃/0.08mmHg (kugelrohr)

IR(film) : 3270. 1640. 1540$cm^{-1}$

NMR($CDCl_3$, $\delta$) : 1.15(3H. t. J=7Hz. $CH_3$).

1.99(3H. s. $COCH_3$). 2.19(2H. m. $NCH_2\underline{CH_2}CH=$).

2.49(2H. quartet. J=7Hz. $N\underline{CH_2}CH_3$).

2.52(2H. t. J=6Hz. $CH_2\underline{CH_2}N$).

2.72(2H. d. J=2.5Hz. $NCH_2C=$).

3.78(2H. d. J=5.5Hz. $CH_2N$). 5.65(1H. m. $HC=$).

5.8(1H. m. NH)

MASS(m/z) : 182($M^+$). 123. 110(base). 108

Preparation 8

4-Acetylaminomethyl-1-benzyl-1,2,3,6-tetrahydropyridine

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was obtained via 4-acetylaminomethyl-1-benzyl-pyridinium bromide by reacting 4-acetylamino-methylpyridine and benzyl bromide as raw materials. In a similar manner to those of Preparations 3 and 4.

IR(Film) : 3250, 1650, 740, 700cm$^{-1}$

NMR(CDCl$_3$, $\delta$) : 1.98(s, 3H), 2.00-2.15(m, 2H),
2.15-2.35(m, 2H), 2.97(br s, 2H), 3.45(s, 2H),
3.95-4.00(m, 2H), 5.53(br s, 1H), 5.84(br s, 1H),
7.20-7.40(m, 5H)

MASS(m/z) : 244(M$^+$), 185, 172

Preparation 9

A solution of 4-acetylaminomethyl-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (5.00 g) and 6N aqueous solution of sodium hydroxide (16 ml) in methanol (32 ml) was refluxed for 23 hours, and then the solvent was evaporated. Ethyl acetate and 1N sodium hydroxide aqueous solution were added to the residue. The organic layer was separated, washed with brine, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silicagel with an eluent of a mixture of methylene chloride and methanol (10:1 - 2:1) to give 4-aminomethyl-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (2.31 g) as an oil.

IR(film) : 3370, 1610, 760, 730cm$^{-1}$

NMR(CDCl$_3$, $\delta$) : 1.84(br s. 2H). 2.13(br s. 2H).
2.57(t. J=5.8Hz. 2H). 2.99(br s. 2H). 3.20(br s. 2H).
3.53(s. 2H). 3.80(s. 3H). 5.53-5.57(m. 1H).
6.80-6.90(m. 2H). 7.20-7.30(m. 2H)

MASS(m/z) : 232($M^+$). 202. 121

Preparation 10

4-Aminomethyl-1-propyl-1,2,3,6-tetrahydropyridine was obtained by reacting 4-acetylaminomethyl-1-propyl-1,2,3,6-tetrahydropyridine as a raw material. in a similar manner to that of Preparation 9.

bp : 140-150 ℃/10mmHg (Kugelrohr)

IR(Film) : 3270. 1600$cm^{-1}$

NMR(CDCl$_3$, $\delta$) : 0.92(t. J=7.3Hz. 3H). 1.10-1.70(br s. 2H).
1.55(t. quartet. J=7.3Hz. J=5.7Hz. 2H).
2.14(d. J=1.6Hz. 2H). 2.30-2.40(m. 2H).
2.57(t. J=5.7Hz. 2H). 2.96-3.00(m. 2H). 3.10(s. 2H).
5.53-5.57(m. 1H)

MASS(m/z) : 154($M^+$). 125. 96

Preparation 11

4-Aminomethyl-1-benzyl-1,2,3,6-tetrahydropyridine was obtained by reacting 4-acetylaminomethyl-1-benzyl-1,2,3,6-tetrahydropyridine as a raw material. in a similar manner to that of Preparation 9.

IR(Film) : 3370. 3270. 1600. 740. 700$cm^{-1}$

NMR(CDCl$_3$, $\delta$) : 1.61(s. 2H). 2.13(br s. 2H).
2.58(t. J=5.8Hz. 2H). 2.95-3.05(m. 2H). 3.20(br s. 2H)
3.59(s. 2H). 5.50-5.55(m. 1H). 7.20-7.37(m. 5H)

MASS(m/z) : 202($M^+$). 172. 97

Preparation 12

3-Aminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine was obtained by reacting 3-acetylaminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine as a raw material, in a similar manner to that of Preparation 9.

bp : 100-105 ℃/8.5mmHg (Kugelrohr)

IR(Nujol) : 3450. 3370. 3280. 3200$cm^{-1}$

NMR(CDCl$_3$, $\delta$) : 1.14(3H. t. J=7Hz. $CH_3$).
1.61(2H. s. $NH_2$). 2.21(2H. m. $CH_2\underline{CH}_2CH$=).
2.47(2H. quartet. J=7Hz. $NC\underline{H}_2CH_3$).
2.49(2H. t. J=6Hz. $NC\underline{H}_2CH_2CH$=). 2.93(2H. m. $CH_2N$).
3.20(2H. m. $CH_2N$). 5.62(1H. m. CH=)

MS(m/z) : 140($M^+$). 123(base). 110. 108

Preparation 13

Acetic anhydride (17.5 ml) was added to a stirred solution of 3-aminomethylpyridine (10.0 g) in acetic acid (30 ml) at room temperature. The resulting mixture was stirred at room temperature for 30 minutes and concentrated in vacuo to afford 3-acetylaminomethylpyridine as a crude oil, which was converted

to 3-acetylaminomethyl-1-ethylpyridinium iodide by reacting with ethyl iodide in a similar manner to that of Preparation 3, and then crystallized from a mixture of n-hexane and ethyl acetate to give pale yellow crystals.

mp : 110-111 ℃

IR(Nujol) : 3420, 3260, 1640cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.54(3H, t, J=7.5Hz, $CH_3$),

1.93(3H, s, $COCH_3$), 4.44(2H, d, J=6Hz, $CH_2NCO$),

4.64(2H, quartet, J=7.5Hz, $NCH_2CH_3$),

8.12(1H, t, J=7.5Hz, pyridinium H),

8.43(1H, d, J=7.5Hz, pyridinium H),

8.59(1H, t, J=6Hz, NH), 9.0(2H, m, pyridinium H)

MASS(m/z) : 135, 107

Preparation 14

A mixture of ethyl 3,3-diphenyl-2-propenoate (4.28 g) in 3N-sodium hydroxide aqueous solution (28 ml) and ethanol (50 ml) was allowed to stand overnight at room temperature and stirred at 50℃ for 2 hours. Ethyl acetate and brine were added to the mixture and the resulting solution was acidified with concentrated hydrochloric acid. The organic layer was separated, dried over magnesium sulfate, and the solvent was evaporated in vacuo to give 3,3-diphenyl-2-propenoic acid.

mp : 158-161 ℃ (washed with ethyl acetate)

IR(Nujol) : 1690, 1660, 1610, 720, 700cm$^{-1}$

NMR(CDCl$_3$, $\delta$) : 6.32(s, 1H), 7.10-7.40(m, 10H)

MASS(m/z) : 224(M$^+$), 179, 165

Example 1

To a solution of 4-[(2-hydroxy-2,2-diphenylacetylamino)methyl]-1-(4-methoxybenzyl)pyridinium chloride (100 g) in methanol (800 ml) was added portionwise sodium borohydride (32.7 g) at 10 - 20 ℃ in a nitrogen atomosphere. The resulting solution was stirred at room temperature for 1 hour, and then the mixture was evaporated. Ethyl acetate (1 ℓ) and water (500 ml) were added to the residue, and the organic layer was separated, washed with water (500 ml), brine (500 ml), dried over magnesium sulfate, and evaporated to give N-[1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridin-4-yl]methyl-2-hydroxy-2,2-diphenylacetamide as crude oil. A mixture of the crude oil and 1-chloroethyl chloroformate (25 ml) in methylene chloride (700 ml) was refluxed for 1 hour. Methanol (350 ml) was added to the mixture. The solution was refluxed for 30 minutes, and the solvent was evaporated. The residue was treated with 4N-hydrogen chloride in ethyl acetate, crystallized and recrystallized from ethanol to give N-(1,2,3,6-tetrahydropyridin-4-yl)-methyl-2-hydroxy-2,2-diphenylacetamide hydrochloride as colorless crystals (41.64).

mp : 222-224 ℃

IR(Nujol) : 3350, 1650, 750, 730, 690cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 2.15(2H, br s), 3.10(2H, t, J=5.9Hz),
3.34(2H, br s), 3.70(2H, d, J=5.5Hz), 5.41(1H, br s),
5.82(1H, s), 7.20-7.45(10H, m), 8.34(1H, t, J=5.5Hz),
9.15(2H, br s)

MASS(m/z) : 322($M^+$), 183, 95

Example 2

2-Hydroxy-2,2-diphenyl-N-[(1,2,3,6-tetrahydro-4-pyridyl)methyl]acetamide (1.00 g) was hydrogenated over 10 % palladium on carbon in methanol. After the catalyst was removed by filtration, the filtrate was evaporated in vacuo and recrystallized from ethanol to give 2-hydroxy-2,2-diphenyl-N-[(piperidine-4-yl)methyl]acetamide hydrochloride (0.35 g).

mp : 251-253 ℃

IR(Nujol) : 3360, 2470, 1650, 1600, 750, 730, 700$cm^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.10-1.40(m, 2H), 1.50-1.80(m, 3H),
2.65-2.90(m, 2H), 2.90-3.10(m, 2H), 3.10-3.30(m, 2H),
6.75(s, 1H), 7.20-7.45(m, 10H), 8.28(br s, 1H),
8.89(br s, 2H)

MASS(m/z) : 324($M^+$), 183, 105

Elemental analysis: $C_{21}H_{24}N_2O_2 \cdot HCl$

Calculated value: C 66.58, H 6.98, N 7.76

Actual value: C 67.04, H 7.09, N 7.76

Example 3

2-Hydroxy-N-[(1-methylpiperidine-4-yl)methyl]-2,2-diphenylacetamide hydrochloride was obtained by reacting N-[(1-methyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2-hydroxy-2,2-diphenylacetamide as a raw material, in a similar manner to that of Example 2.

mp : 237-239 ℃

IR(Nujol) : 3430, 3150, 1670, 790, 770, 710, 700cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.20-1.50(m, 1H), 1.60-1.80(m, 2H),
2.20-3.20(m, 8H), 2.68(s, 3H), 6.73(s, 1H),
7.20-7.35(m, 10H), 8.30(br s, 1H), 9.70-9.90(br s, 1H)

MASS(m/z) : 338($M^+$), 183, 105

Elemental analysis: $C_{21}H_{26}N_2O_2 \cdot HCl$

Calculated value: C 67.28, H 7.26, N 7.47

Actual value: C 67.64, H 7.56, N 7.53

Example 4

A solution of 2,2-diphenyl-2-hydroxy-N-[[1-(4-methoxybenzyl)-1,2,3,6-tetraphydropyridine-4-yl]methyl]acetamide (1.03 g) and benzyl chloroformate (0.437 g) in 1,2-dichloroethane (10 ml) was stirred at room temperature for 4 hours, diluted with water, and extracted with methylene chloride. The extract was dried over magnesium sulfate, evaporated in vacuo, and chromatographed over silica gel using methylene chloride-methanol as an eluent to afford N-[(1-benzyloxycarbonyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2,2-diphenyl-2-hydroxy-acetamide

(0.797 g) as an oil.

IR(film) : 3390, 1690, 1670cm$^{-1}$

NMR(CDCl$_3$, $\delta$) : 1.99(2H, br s, =CCH$_2$CH$_2$N),

3.52(2H, t, J=5.5Hz, CH$_2$CH$_2$NCOO), 3.76(1H, s, OH),

3.90(4H, m, =CHCH$_2$NCOO and CONCH$_2$), 5.13(2H, s, OCH$_2$),

5.37(1H, br s, =CH), 5.49(1H, m, CONH),

7.3-7.5(15H, m, aromatic H)

MASS(m/z) : 183, 105, 91, 77

Example 5

A mixture of N-[[1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine-4-yl]methyl]-2,2-diphenyl-2-hydroxy acetamide (2.77 g) and 1-chloroethyl chloroformate (0.75 ml) in 1,2-dichloroethane (55 ml) was refluxed for 30 minutes. Methanol (50 ml) was added to the mixture, and the solution was refluxed for 1 hour and evaporated. The residue was purified by column chromatography on silica gel with a mixture of dichloromethane and methanol (10:1), methanol, and then a mixture of methanol and 28 % ammonia water (10:1), successively, as an eluent. The eluate was evaporated. The residue was treated with 4N-hydrogen chloride in ethyl acetate, crystallized, and recrystallized from methanol and ethyl acetate to give N-[[1,2,3,6-tetrahydropyridine-4-yl]methyl]-2,2-diphenyl-2-hydroxy acetamide hydrochloride as colorless crystals (1.33 g).

mp : 223-224 ℃

IR(Nujol) : 3350, 1650, 750, 730, 690cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 2.15(br s, 2H), 3.10(t, J=5.9Hz, 2H),
3.34(br s, 2H), 3.70(d, J=5.5Hz, 2H), 5.41(br s, 1H),
6.82(s, 1H), 7.20-7.45(m, 10H), 8.34(t, J=5.5HZ, 1H),
9.15(br s, 2H)

MASS(m/z) : 322($M^+$), 183, 95

Example 6

A solution of N-[(1-benzyloxycarbonyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2,2-diphenyl-2-hydroxyacetamide (156 mg) in 25 % hydrogen bromide-acetic acid solution (1.86 ml) was stirred for 30 minutes under ice cooling and for 3 hours at room temperature, and then evaporated in vacuo. The residue was partitioned between diisopropyl ether and water. The aqueous layer was separated, basified with 1N sodium hydroxide solution, and extracted with methylene chloride. The methylene chloride layer was washed with brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by column chromatography on silica gel using methylene chloride-methanol as an eluent to afford 2,2-diphenyl-2-hydroxy-N-[(1,2,3,6-tetrahydropyridine-4-yl)methyl]acetamide (85 mg) as a colorless powder, which was recrystallized with ethanol.

mp : 151-153 ℃

Elemental analysis:

Calculated value: C 74.51, H 6.88, N 8.69

Actual value: C 74.59, H 7.08, N 8.74

IR(Nujol) : 3380, 3300, 1570$cm^{-1}$

NMR($CDCl_3$, $\delta$) : 1.95(2H, m, -CCH$_2$CH$_2$NH).

2.85(2H, t, J=5.5Hz, CH$_2$CH$_2$NH).

3.23(2H, br s, -CH$_2$CH$_2$NH). 3.35(2H, br, -NH and OH).

3.84(2H, d, J=5.5Hz, CONHCH$_2$). 5.44(1H, br s, =CH).

6.70(1H, t, J=5.5Hz, CONH).

7.25-7.5(10H, m, aromatic H)

MASS(m/z) : 322($M^+$), 183(base), 105(base), 96(base)

Example 7

To a solution of N-[(1,2,3,6-tetrahydropyridin-4-yl)methyl]-2,2-diphenyl-2-hydroxy acetamide (6.00 g) in methanol (60 ml) was added a solution of methanol (20 ml) at room temperature. The resulting solution was evaporated in vacuo and the residue was crystallized and recrystallized from ethanol to give N-[(1,2,3,6-tetrahydropyridine-4-yl)methyl]-2,2-diphenyl-2-hydroxyacetamide methanesulfonate as colorless crystals (6.66 g).

mp : 195-197 ℃

IR(Nujol) : 3400, 1670, 1590, 780, 750, 740, 700$cm^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 2.14(br s, 2H), 2.31(s, 3H),

3.14(t, J=6.1Hz, 2H), 3.51(br s, 2H),

3.71(d, J=6.1Hz, 2H), 5.40(br s, 1H), 6.81(s, 1H),

7.20-7.41(m, 10H), 8.36(t, J=6.1Hz, 1H),

8.65(br s, 2H)

MASS(m/z) : 323(M+1)

Elemental analysis: $C_{20}H_{22}N_2O_2 \cdot CH_4SO_3H$

Calculated value: C 60.27, H 6.26, N 6.69, S 7.66

Actual value: C 60.32, H 6.32, N 6.62, S 7.86

Example 8

A mixture of N-(1-ethoxycarbonylpiperidine-4-yl)-2,2-diphenylacetamide (4.00 g) and potassium hydroxide (2.0 g) in methyl cellosolve (30 ml) was refluxed for 3.5 hours. Ethyl acetate (100 ml) and water (300 ml) were added to the mixture and resulting solution was separated. The aqueous layer was extracted with ethyl acetate (100 ml x 3). The combined organic layers were evaporated in vacuo and treated with 4N hydrogen chloride in ethyl acetate to give N-(piperidine-4-yl)-2,2,-diphenylacetamide hydrochloride.

mp : 233-235 ℃ (washed with ethyl acetate)

IR(Nujol) : 3500, 3300, 1630, 740, 720cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.45-1.75(m, 2H), 1.75-2.00(m, 2H),
2.80-3.10(m, 2H), 3.10-3.25(m, 2H), 3.70-3.95(m, 1H)
4.97(s, 1H), 7.10-7.40(m, 10H), 8.59(d, J=7.4Hz, 1H),
8.86(br s, 2H)

MASS(m/z) : 294($M^+$), 220, 167, 127

Elemental analysis: $C_{19}H_{22}N_2O \cdot HCl$

Calculated value: C 65.41, H 7.22, N 8.03

Actual value: C 65.87, H 7.32, N 8.12

Example 9

2-Hydroxy-N-(piperidine-4-yl)-2,2-diphenylacetamide hydrochloride was obtained by reacting N-(1-ethoxycarbonylpiperidin-4-yl)-2-hydroxy-2,2-diphenylacetamide as a raw material, in a similar manner to that of Example 8.

mp : 193-195 ℃ (washed with acetone)

IR(Nujol) : 3300, 2700, 2600, 2470, 1660, 770, 750, 730, 700 $cm^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.60-2.00(m, 4H), 2.75-3.05(m, 2H), 3.05-3.30(m, 2H), 3.75-4.00(m, 1H), 6.77(s, 1H), 7.20-7.95(m, 10H), 8.15(d, J=7.7Hz, 1H), 8.94(br s, 1H), 9.10(br s, 1H)

MASS(m/z) : (no $M^+$), 183, 105

Elemental analysis: $C_{19}H_{21}N_2O_2 \cdot HCl$

| | | | | |
|---|---|---|---|---|
| Calculated value: | C 64.67, | H 6.76, | N 7.94, | Cl 10.05 |
| Actual value: | C 64.79, | H 6.93, | N 7.92, | Cl 9.98 |

Example 10

A solution of N-(pyridine-4-yl)methyl-2-hydroxy-2,2-diphenylacetamide (2.00 g) and methyl iodide (1.6 ml) in acetone (100 ml) was refluxed for 3 hours and evaporated to give 1-methyl-4-[(2-hydroxy-2,2-diphenylacetylamino)-methyl]pyridinium iodide as a crude oil. The oil was dissolved in methanol (50 ml), and sodium borohydride (0.95 g) was added to the solution. The resulting mixture was stirred for 1 hour at room temperature, and then evaporated. The residue was partitioned between ethyl ace-

tate and 1N sodium hydroxide solution. The organic layer was separated, washed with water, brine, dried over magnesium sulfate, and evaporated. The residue was treated with 4N-hydrogen chloride in ethyl acetate, crystallized and recrystallized from 2-propanol and methanol to give N-(1-methyl-1,2,3,6-tetrahydropyridine-4-yl)methyl-2-hydroxy-2,2-diphenylacetamide (0.41 g).

mp: 173-174 ℃

IR(Nujol) : 3340, 3200, 2550, 1660, 770, 750, 720, 700cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 2.00-2.50(2H, m), 2.80-3.90(4H, m),
2.73(3H, s), 3.72(2H, d, J=6.1Hz), 5.38(1H, s),
6.82(1H, s), 7.20-7.40(10H, m), 8.37(1H, t, J=6.1Hz)
10.77(1H, br s)

MASS(m/z) : 336($M^+$), 183, 109

Example 11

N-(1-ethylpyridinio-4-yl)methyl-2-hydroxy-2,2-diphenylacetamide iodide was obtained by reacting N-(pyridine-4-yl)methyl-2-hydroxy-2,2-diphenylacetamide and methyl iodide as raw materials, in a similar manner to that of Example 10.

mp: 123-124 ℃

IR(Nujol) : 3350, 1650, 780, 740, 720, 700cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.52(t, J=7.2Hz, 3H), 4.57(q, J=7.2Hz, 2H)
4.60(d, J=6.0Hz, 2H), 7.00(s, 1H), 7.20-7.50(m, 10H),
7.85(d, J=6.6Hz, 2H), 9.01(d, J=6.6Hz, 2H),

9.13(t, J=6.0Hz, 1H)

MASS(m/z) : (no M$^+$) , 183, 105

Example 12

A mixture of 2-hydroxy-2,2-diphenyl-N-[(1,2,3,6-tetrahydropyridine-4-yl)methyl]acetamide hydrochloride (0.70 g) and sodium cyanoborohydride (0.18 g) in dry methanol (15 ml) and dry acetone (5 ml) was stirred for 4 days at room temperature, and then the mixture was evaporated in vacuo. Ethyl acetate and 1N sodium hydroxide solution were added to the residue. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was treated with 4N-hydrogenchloride in 1,4-dioxane, and crystallized to give 2-hydroxy-N-[(1-isopropyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2,2-diphenylacetamide hydrochloride (0.58 g).

mp : 126-127 ℃ (washed with 1,4-dioxane)

IR(Nujol) : 3250, 1660, 760, 700cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.26(d, J=6.6Hz, 6H), 2.05-2.25(m, 1H),
2.30-2.60(m, 1H), 2.75-3.10(m, 1H), 3.25-3.50(m, 2H),
3.58(br s, 2H), 3.73(d, J=6.0Hz, 2H), 5.42(s, 1H),
6.83(br s, 1H), 7.15-7.60(m, 10H), 8.36(t, J=6.0Hz,1H)
10.30(br s, 1H)

Elemental analysis: $C_{28}H_{30}N_2O_2 \cdot HCl \cdot 1/2H_2O$

Calculated value: C 67.39, H 7.38, N 6.83, Cl 8.65

Actual value: C 67.40, H 7.84, N 6.58, Cl 8.35

Example 13

N-(1-ethylpiperidine-4-yl)-2-hydroxy-2,2-diphenylacetamide fumarate was obtained by reacting N-(piperidine-4-yl)-2-hydroxy-2,2-diphenylacetamide as a raw material, in a similar manner to that of Example 12.

mp: 197-199 ℃ (recrystallization from isopropyl alcohol)

IR(Nujol) : 3420, 2350, 1670, 750, 700, 670cm$^{-1}$

NMR(DMSO-d$_6$, $\delta$) : 1.05(t, J=7.2Hz, 3H), 1.45-1.65(m, 4H),
2.15-2.40(m, 2H), 2.54(q, J=7.2Hz, 2H),
2.85-3.05(m, 2H), 3.55-3.75(m, 1H), 6.50(s, 1H),
7.20-7.40(m, 11H), 7.96(d, J=8.0Hz, 1H)

Elemental analysis: $C_{21}H_{24}N_2O \cdot 1/2C_4H_4O_4 \cdot 1/2H_2O$

Calculated value: C 68.13, H 7.21, N 6.91

Actual value: C 67.97, H 7.41, N 6.67

Example 14

N-(1-isopropylpiperidine-4-yl)-2,2-diphenylacetamide fumarate was obtained by reacting N-(piperidine-4-yl)-2,2-diphenyl-acetamide hydrochloride as a raw material, in a similar manner to that of Example 12.

mp: 175-177 ℃ (washed with acetone)

IR(Nujol) : 3200, 2650, 2500, 1660, 790, 770, 740, 700cm$^{-1}$

NMR(DMSO-d$_6$, $\delta$) : 1.13(d, J=6.6Hz, 6H), 1.45-1.75(m, 2H),

1.75-2.00(m. 2H). 2.65-2.90(m. 2H). 3.00-3.25(m. 3H).

3.65-3.90(m. 1H). 4.93(s. 1H). 6.54(s. 3H).

7.10-7.35(m. 10H). 8.43(d. J=7.3Hz. 1H)

MASS(m/z) : 336($M^+$). 321. 167

Elemental analysis: $C_{23}H_{24}N_2O \cdot 3/2(C_4H_4O_4)$

Calculated value: C 65.87. H 6.71. N 5.49

Actual value: C 65.60. H 6.84. N 5.57

Example 15

N-(1-ethylpiperidine-4-yl)-2,2-diphenylacetamide fumarate was obtained by reacting N-(piperidine-4-yl)-2,2-diphenylacetamide hydrochloride as a raw material, in a similar manner to that of Example 12.

mp : 179-181 ℃ (washed with acetone)

IR(Nujol) : 3250. 1690. 1760. 790. 760. 740$cm^{-1}$

NMR(DMSO-$d_6$. $\delta$) : 1.05(t. J=7.2Hz. 3H). 1.30-1.60(m. 2H).

1.70-1.85(m. 2H). 2.25-2.40(m. 2H).

2.55(q. J=7.2Hz. 2H). 2.90-3.10(m. 2H).

3.40-3.55(m. 1H). 4.91(s. 1H). 6.55(s. 2H).

7.20-7.30(m. 10H). 8.34(d. J=7.4Hz. 1H)

MASS(m/z) : 322($M^+$). 307. 167. 111

Elemental analysis: $C_{21}H_{26}N_2O \cdot C_4H_4O_4 \cdot 1/2H_2O$

Calculated value: C 67.10. H 6.98. N 6.26

Actual value: C 66.78. H 6.97. N 6.05

Example 16

A mixture of benzylic acid (2.21 g) and 1,1'-carbonyldiimidazole (1.73 g) in dry dichloromethane (45 ml) was stirred for 2.5 hours at room temperature. Then 4-aminomethyl-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (2.25 g) in dry dichloromethane (20 ml) was added dropwise over 20 minutes. The mixture was stirred for 45 minutes at room temperature and evaporated. Ethyl acetate and 1N sodium hydroxide were added to the residue. The organic layer was separated, washed twice with water, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with a mixture of dichloromethane and methanol (10:1) as an eluent to give N-[[1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine-4-yl]methyl]-2,2-diphenyl-2-hydroxyacetamide (3.47 g) as a pale yellow oil.

IR($CHCl_3$) : 3370, 1660, 1610, 750, 730, 700$cm^{-1}$

NMR($CDCl_3$, $\delta$) : 2.02(br s, 2H), 2.52(t, J=5.8Hz, 2H),
2.91(br s, 2H), 3.50(s, 2H), 3.80(s, 3H),
4.10(br s, 1H), 4.14(s, 2H), 5.39(br s, 1H),
6.39(br s, 1H), 6.85(d, J=12.7Hz, 2H),
7.20-7.50(m, 12H)

MASS(m/z) : 442($M^+$), 202, 121

Example 17

N-[(1-methyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2,2-diphenyl-2-hydroxyacetamide oxalate was obtained by reacting benzylic acid and 1-methyl-4-aminomethyl-1,2,3,6-tetrahydropyri-

dine as raw materials, in a similar manner to that of Example 16.

mp : 1 5-190 ℃

IR(Nujol) : 1650, 1600, 770, 750, 730, 700cm$^{-1}$

NMR(DMSO-d$_6$, $\delta$) : 2.09(br s, 2H), 2.50(s, 3H),
2.81(t, J=5.9Hz, 2H), 3.19(br s, 2H),
3.68(d, J=6.0Hz, 2H), 4.98(br, 2H), 5.37(s, 1H),
7.20-7.45(m, 11H), 8.26(t, J=6.0Hz, 1H)

MASS(m/z) : 336(M$^+$), 215, 183, 109

Example 18

2-Hydroxy-2,2-diphenyl-N-[(1-propyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]acetamide hydrochloride was obtained by reacting benzylic acid and 1-propyl-4-aminomethyl-1,2,3,6-tetrahydropyridine as raw materials, in a similar manner to that of Example 16.

mp : 96-98 ℃ (recrystallization from a mixture of ethyl acetate-methanol-diisopropyl ether)

IR(Nujol) : 3250, 1660, 770, 740, 700cm$^{-1}$

NMR(DMSO-d$_6$, $\delta$) : 0.89(t, J=7.3Hz, 3H), 1.60-1.80(m, 2H),
2.00-2.55(m, 2H), 2.90-4.20(m, 8H), 5.89(br s, 1H),
6.82(s, 1H), 7.20-7.45(m, 10H), 8.37(t, J=6.1Hz, 1H),
10.50(br s, 1H)

MASS(m/z) : 364(M$^+$), 335, 183, 137

Elemental analysis: $C_{23}H_{28}N_2O_2 \cdot HCl$

Calculated value: C 66.80, H 7.41, N 6.77, Cl 9.57

Actual value: C 66.77, H 7.76, N 6.44, Cl 8.57

Example 19

N-[(1-benzyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2-hydroxy-2,2-diphenylacetamide hydrochloride was obtained by reacting benzylic acid and 1-benzyl-4-aminomethyl-1,2,3,6-tetrahydropyridine as raw materials, in a similar manner to that of Example 16.

mp: 139-141 ℃ (recrystallization from a mixture of methanol-ethyl acetate-diisopropyl ether)

IR(Nujol) : 3450, 3200, 2570, 1660, 750, 710, 680cm$^{-1}$

NMR(DMSO-d$_6$, $\delta$) : 2.00-2.50(m, 2H), 2.70-3.50(m, 2H),
3.50(br s, 2H), 3.72(d, J=6.0Hz, 2H), 4.30(s, 2H),
5.38(s, 1H), 6.81(s, 1H), 7.25-7.63(m, 15H),
8.36(t, J=6.0Hz, 1H), 10.92(br s, 1H)

Elemental analysis: $C_{33}H_{33}N_3O_2 \cdot HCl$

Calculated value: (as 0.8 $H_2O$)
C 69.98, H 6.66, N 6.05, Cl 7.65

Actual value: C 69.94, H 6.67, N 5.94, Cl 7.63

Example 20

N-[(1-ethyl-1,2,3,6,-tetrahydropyridine-3-yl)methyl]-2,2-diphenyl-2-hydroxyacetamide 1/2 fumarate was obtained by reacting benzylic acid and 1-ethyl-3-aminomethyl-1,2,3,6-tetrahydropyridine as raw materials, in a similar manner to that of Example 16.

mp: 185-186 ℃ (recrystallization from isopropyl alcohol)

IR(Nujol) : 3400, 2750-2600, 1675, 1590cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.02(3H, t, J=7Hz, $CH_3$),

2.09(2H, m, $-CH\underline{CH}_2CH_3$), 2.45-2.65(4H, m, $NCH_2 \times 2$),

2.92(2H, s, $-CCH_2N$), 3.68(2H, m, $CONCH_2$),

5.52(1H br s, =CH), 6.51(2H, s, fumaric acid-CH),

7.25-7.4(10H, m, aromatic H), 8.21(1H, br s, CONH)

MASS(m/z) : 350($M^+$), 183, 124(base), 105

Elemental analysis: $C_{21}H_{22}N_2O_2 \cdot 1/2C_4H_4O_4$

| | | | | | |
|---|---|---|---|---|---|
| Calculated value: | C | 70.57, | H | 6.91, | N 6.86 |
| Actual value: | C | 70.36, | H | 7.11, | N 6.72 |

Example 21

To a mixture of 4,4'-difluorobenzophenone (2.0 g) and zinc iodide (0.1 g) in dry dichloromethane (15 ml) was added trimethylsilyl cyanide (1.35 ml) at room temperature. The resulting mixture was stirred for 40 hours at the same temperature, and then the solvent was evaporated in vacuo. Concentrated hydrochloric acid (30 ml) was added to the residue and the mixture was stirred at 90 ℃ for 14 hours. The mixture was partitioned between ethylacetate and water. The organic layer was separated and evaporated in vacuo. The residue was partitioned between diisopropylether and 1N aqueous sodium hydroxide. The organic layer was washed with 1N aqueous sodium hydroxide three times. The combined aqueous layers were acidified with concentrated hydrochloric acid and extracted with ethyl acetate twice.

The combined organic layers were washed with water and brine, dried over magnesium sulfate and evaporated in vacuo to give crude 4,4'-difluorobenzilic acid (0.80 g). To a solution of this crude 4,4'-difluorobenzilic acid (0.80 g) and N,N'-carbonyldiimidazole (0.60 g) in dry dichloromethane was added dropwise a solution of 4-aminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine (0.60 g) in dichloromethane at room temperature.

The resulting mixture was stirred at room temperature, evaporated in vacuo. The residue was partitioned between ethylacetate and 1N aqueous sodium hydroxide. The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel and then on alumina and treated with 4N hydrogenchloride in ethylacetate to give 2,2-bis(4-fluorophenyl)-2-hydroxy-N-[(1-ethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]acetamide hydrochloride.

mp : 155-157 ℃ (washed with diisopropyl ether)

IR(Nujol) : 3350, 3270, 2500, 1660, 1600, 820, 770cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.24(t, J=7.2Hz, 3H), 2.00-2.45(m, 2H),
2.85-3.80(m, 6H), 3.09(quartet, J=7.2Hz, 2H),
5.39(s, 1H), 6.96(s, 1H), 7.10-7.20(m, 4H),
7.35-7.45(m, 4H), 8.46(br s, 1H), 10.21(br s, 1H)

MASS(m/z) : 388($M^+$), 371, 219, 123, 110

Elemental analysis: $C_{21}H_{24}N_2O_2F_2 \cdot HCl \cdot 1/3H_2O$

Calculated value: C 61.61, H 6.03, N 6.53, Cl 8.27

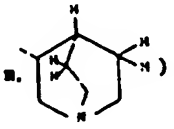
Actual value: C 61.69, H 6.09, N 6.54, Cl 8.27

Example 22

A solution of 3-amino-1-azabicyclo[2.2.2]octane in benzene (12 ml) was added dropwise to a stirred solution of 2-chloro-2,2-diphenylacetyl-chloride (6.30 g) in benzene (17 ml)-n-hexane (11 ml) at room temperature. The resulting mixture was stirred for 3 hours and 30 minutes at room temperature and partitioned between toluene and water. The organic layer was extracted twice with 1N hydrochloric acid and the aqueous layers were combined, washed with diethyl ether, stirred at 70 ℃ for 1 hour, cooled with ice water, basified with 5 % sodium hydroxide aqueous solution, and extracted twice with ethyl acetate. The ethyl acetate layers were combined, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was washed with diisopropyl ether to afford a colorless powder (2.90 g), which was converted to the hydrochloride in a usual manner. The hydrochloride was recrystallized from ethanol to afford N-(1-azabicyclo[2.2.2.]octan-3-yl)-2,2-diphenyl-2-hydroxyacetamide hydrochloride as a colorless powder.

mp : 261-265 ℃ (dec.)

IR(Nujol) : 3300, 2800-2300, 1660cm$^{-1}$

NMR(DMSO-d$_6$, δ) : 1.6-2.1(5H, m,  ),

3.05-3.6(6H, m, N(CH$_2$)$_3$), 4.15(1H, m, CONHCH),

6.87(1H, S, OH), 7.25-7.45(10H, m, aromatic H).

8.59(1H. d. J=7Hz. CONH). 10.36(1H. br s. HCl)

MASS(m/z) : 336($M^+$). 183(base). 105

Elemental analysis: $C_{21}H_{24}N_2O_3 \cdot HCl$

Calculated value: C 67.64. H 6.76. N 7.51

Actual value: C 67.67. H 7.10. N 7.31

Example 23

N-(1-ethoxycarbonylpiperidine-4-yl)-2-hydroxy-2,2-diphenyl acetamide was obtained by reacting 4-amino-1-ethoxycarbonylpiperidine and benzylic acid as raw materials, in a similar manner to that of Example 16.

mp: 128-131 ℃ (washed with n-hexane)

IR(Nujol) : 3300. 1650. 1620. 760. 740. 720$cm^{-1}$

NMR($CDCl_3$, $\delta$) : 1.00-1.41(m. 2H). 1.23(t. J=7.1Hz. 3H).

1.70-2.00(m. 2H). 2.75-3.00(m. 2H). 3.30-4.20(m. 3H).

4.08(q. J=7.1Hz. 2H). 6.87(d. J=8.0Hz. 1H).

6.93(s. 1H). 7.20-7.50(m. 10H)

MASS(m/z) : 382($M^+$). 370. 216. 183

Example 24

2,2-Diphenyl-2-hydroxy-N-[2-(1-methylpiperidine-4-yl)-ethyl]acetamide fumarate was obtained by reacting 4-(2-aminoethyl)-1-methylpiperidine and benzylic acid as raw materials, in a similar manner to that of Example 16. The residue was chromatographed over silica gel using chloroform - methanol as an eluent to afford white powder.

mp : 151-152 ℃

IR(Nujol) : 3360, 3250, 3200, 2740-2100, 1700, 1670cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.15-1.45(5H, m, CH and $CH_2$ × 2),

1.7(2H, m, $CH_2$), 2.35(2H, m, $CH_2$), 2.45(3H, s, $CH_3$),

3.0-3.2(4H, m, $CH_2$ × 2), 6.50(2H, s, HC=CH),

7.2-7.4(11H, m, aromatic H and OH),

8.15(1H, t, J=6Hz, NH)

MASS(m/z) : 352($M^+$), 337, 183(base)

Elemental analysis: $C_{21}H_{24}N_2O_2 \cdot C_4H_4O_4$

Calculated value: C 66.65, H 6.88, N 5.93

Actual value: C 67.02, H 7.05, N 5.94

Example 25

N-[(1-ethylpiperidine-3-yl)methyl]-2,2-diphenyl-2-hydroxyacetamide hydrochloride as a colorless crystallization was obtained by reacting 3-aminomethyl-1-ethylpiperidine and benzylic acid as raw materials, in a similar manner to that of Example 16.

free base:

IR(Nujol) : 3310, 2800-2300, 1660cm$^{-1}$

NMR($CDCl_3$, $\delta$) : 0.95(1H, m, piperidine H),

1.00(3H, t, J=7Hz, $CH_3$), 1.5-1.95(6H, m, piperidine H)

2.30(2H, quartet, J=7Hz, $NCH_2CH_3$),

2.7(2H, m, piperidine H), 3.1-3.35(2H, m, $CONCH_2$),

4.15(1H, br, OH), 6.86(1H, br t, NH),

7.25-7.53(10H, m, aromatic H)

MASS(m/z) : 352($M^+$). 337. 183. 105(base)

hydrochloride:

mp : 181-182 ℃ (recrystallization from isopropyl alcohol)

IR(Nujol) : 3360. 3220. 2660. 2570. 1655$cm^{-1}$

NMR(DMSO-$d_6$. $\delta$) : 1.05(1H. m. piperidine H).

1.16(3H. t. J=7Hz. $CH_3$). 1.75(3H. m. piperidine H).

2.1(1H. m. piperidine H). 2.45(1H. m. piperidine H).

2.7(1H. m. piperidine H).

2.95-3.35(6H. m. $NCH_2CH_2$. piperidine H. and $CONCH_2$).

6.79(1H. s. OH). 7.2-7.45(10H. m. aromatic H).

8.40(1H. t. J=6Hz. NH). 10.2(1H br. HCl)

MASS(m/z) : 352($M^+$). 337. 183. 105(base)

Elemental analysis: $C_{21}H_{25}N_2O_2 \cdot HCl$

Calculated value: C 67.94. H 7.52. N 7.70

Actual value: C 67.76. H 7.68. N 7.15

Example 26

2-Hydroxy-N-[2-(1-methylpyrolidine-2-yl)ethyl]-2.2-diphenylacetamide hydrochloride was obtained by reacting 2-(2-aminoethyl)-1-methylpyrrolidine and benzylic acid as raw materials in a similar manner to that of Example 16.

mp : 155-157 ℃ (recrystallization from a mixture of ethanol and ethyl acetate)

IR(Nujol) : 3400. 3180. 2620. 1660. 770$cm^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.40-1.95(m, 4H), 1.95-2.25(m, 2H),
2.64(s, 3H), 2.75-3.10(m, 2H), 3.10-3.25(m, 2H),
3.75-3.55(m, 1H), 6.76(s, 1H), 7.20-7.50(m, 10H),
8.38(br s, 1H), 10.36(br s, 1H)

MASS(m/z) : 338($M^+$), 323, 183, 155, 84

Elemental analysis: $C_{21}H_{26}N_2O_2 \cdot HCl$

Calculated value: C 67.28, H 7.26, N 7.47, Cl 9.46

Actual value: C 67.29, H 7.53, N 7.46, Cl 9.44

Example 27

N-(1-ethoxycarbonylpiperidine-4-yl)-2,2-diphenylacetamide was obtained by reacting 4-amino-1-ethoxycarbonylpiperidine and benzylic acid as raw materials, in a similar manner to that of Example 16.

mp : 163-165 ℃ (washed with n-hexane)

IR(Nujol) : 3300, 1650, 770, 750, 730, 700$cm^{-1}$

NMR($CDCl_3$, $\delta$) : 1.10-1.35(m, 5H), 1.80-2.00(m, 2H),
2.80-2.95(m, 2H), 3.90-4.15(m, 5H), 4.90(s, 1H),
5.52(d, J=7.5Hz, 1H), 7.20-7.40(m, 10H)

MASS(m/z) : 366($M^+$), 199

Example 28

N-[(1-ethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-3,3-diphenylpropionamide oxalate was obtained by reacting 4-aminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine and diphenylpropion acid as raw materials, in a similar manner to that of Example 16.

(

mp : 133-134 ℃ (recrystallization from a mixture of isopropyl alcohol and diisopropyl ether)

IR(Nujol) : 3330, 2600, 1720, 1540, 1600, 750, 710cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.18(t, J=7.2Hz, 3H), 1.95(br s, 2H), 2.89(d, J=8.2Hz, 2H), 3.01(q, J=7.2Hz, 2H), 2.95-3.10(m, 2H), 3.39(br s, 2H), 3.54(br s, 2H), 4.47(t, J=8.4Hz, 1H), 4.88(s, 1H), 7.10-7.30(m, 10H), 8.13(br s, 1H)

MASS(m/z) : 348($M^+$), 333, 167, 123

Elemental analysis: $C_{22}H_{24}N_2O \cdot C_2H_2O_4$

| | | | | | |
|---|---|---|---|---|---|
| Calculated value: | C | 68.47, | H | 6.90, | N 6.39 |
| Actual value: | C | 68.46, | H | 6.97, | N 6.31 |

Example 29

N-[(1-ethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-3,3-diphenyl acrylamide oxalate was obtained by reacting 4-aminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine and 3,3-diphenylpropene acid as raw materials, in a similar to that of Example 16.

mp : 163-164 ℃ (recrystallization from a mixture of isopropyl alcohol, ethyl acetate and methanol)

IR(Nujol) : 3330, 2720, 1720, 1640, 770, 700cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.20(t, J=7.3Hz, 3H), 2.11(br s, 2H), 3.08(q, J=7.3Hz, 2H), 3.00-3.20(m, 2H), 3.51(br s, 2H) 3.55-3.70(m, 2H), 4.40(br s, 2H), 5.22(s, 1H), 6.50(s, 1H), 7.10-7.40(m, 10H), 8.15-8.20(m, 1H)

MASS(m/z) : 346($M^+$). 207. 123

Elemental analysis: $C_{21}H_{22}N_2O \cdot C_4H_4O_4$

Calculated value: C 68.79 . H 6.47. N 6.42

Actual value: C 69.21 . H 6.53. N 6.40

Example 30

N-[(1-ethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-10,11-dihydro-5-hydroxy-5H-dibenzo[a,d]cycloheptene-5-carboxamide hydrochloride was obtained by reacting 4-aminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine and 5-hydroxy-5H-10,11-dihydrobenzo[a,d,]cycloheptene-5-carboxylic acid as raw materials, in a similar manner to that of Example 16.

free base: colorless crystals

IR(Nujol) : 3460. 3390. 2740. 1640$cm^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 0.98(3H. t. J=7Hz. $CH_3$).

1.86(2H. br s. $\underline{CH_2}CH_2N$).

2.25-2.45(4H. m. $CH_2\underline{CH_2}N\underline{CH_2}CH_2$).

2.75-2.9(4H. m. $=CH\underline{CH_2}N$ and cycloheptene $CH_2$).

3.3-3.45(2H. m. cycloheptene $CH_2$).

3.54(2H. d. J=6Hz. $CONCH_2$). 5.29(1H. s. =CH).

6.81(1H. s. OH). 7.05-7.25(6H. m. aromatic H).

7.46(1H. t. J=6Hz. NH). 7.75-7.85(2H. m. aromatic H)

MASS(m/z) : 376($M^+$). 209. 123(base). 110

hydrochloride: colorless crystals

mp: 158-159.5 ℃ (ethyl acetate crystals)

IR(Nujol) : 3420, 3330, 2730-2000, 1655cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.23(3H, t, J=7Hz, $CH_3$),

1.95-2.45(2H, m, $\underline{CH}_2CH_2N$),

2.75-3.15(5H, m, $NCH_2CH_2$, cycloheptene $CH_2$, and pyridine H), 3.3-3.45(4H, m, pyridine H×2 and cycloheptene $CH_2$),

3.35-3.65(3H, m, $CONCH_2$ and pyridine H×2),

5.30(1H, br s, =CH), 6.89(1H, s, OH),

7.05-7.25(6H, m, aromatic H),

7.75-7.85(3H, m, NH and aromatic H×2),

10.5(1H, br, HCl)

MASS(m/z) : 376($M^+$), 209(base), 123, 110

Elemental analysis: $C_{23}H_{28}N_2O_2Cl\cdot 3/2H_2O$

Calculated value: C 65.52, H 7.27, N 6.37, Cl 8.06

Actual value: C 65.68, H 7.27, N 6.38, Cl 8.06

Example 31

A solution of 2,2-diphenyl propionic acid (0.70 g) in thionyl chloride (2.3 ml) was refluxed for 2 hours and evaporated in vacuo. Toluene (10 ml) was added to the residue and evaporated in vacuo. To a solution of the residue in dry dichloromethane (10 ml) was added dropwise a mixture of 4-aminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine (0.43 g) and triethylamine (1.5 ml) in dry dichloromehthane (10 ml) at room temperature. The resulting mixture was stirred for 3 hours at room temperature. Dichloromethane and water were added to the

reaction mixture, and then the organic layer was separated, washed successively with water three times, 1N aqueous sodium hydroxide solution, and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of dichloromethane and methanol (20:1) as an eluent, treated with 4N hydrogen chloride in ethyl acetate, recrystallized from isopropyl alcohol and isopropyl ether to give N-[(1-ethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2,2-diphenyl propionamide hydrochloride.

mp: 93-94 ℃

IR(Nujol) : 3450, 3350, 2670, 2600, 1630, 760, 740cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.24(t, J=7.2Hz, 3H), 1.89(s, 3H),

2.00-3.70(m, 8H), 3.06(q, J=7.2Hz, 2H), 5.31(br s, 1H)

7.10-7.40(m, 10H), 7.64(br s, 1H), 10.08(br s, 1H)

Elemental analysis: $C_{24}H_{30}N_2O \cdot HCl$

Calculated value: C 68.56, H 7.75, N 6.95, Cl 8.80

Actual value: C 68.82, H 7.95, N 6.89, Cl 8.95

Example 32

N-[(1-ethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-2,2,-diphenyl acetamide hydrochloride was obtained by reacting 4-aminomethyl-1-ethyl-1,2,3,6-tetrahydropyridine and 2,2-diphenyl acetyl chloride as raw materials, in a similar manner to that of Example 31.

mp: 205-207 ℃ (recrystallization from a mixture of ethanol and diisopropyl ether)

IR(Nujol) : 3270. 3070. 2670. 2550. 2470. 1640. 750. 700cm$^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 1.23(t. J=7.2Hz. 3H). 2.00-2.40(m. 2H).
2.80-3.00(m. 4H). 3.04(q. J=7.2Hz. 2H).
3.60-3.80(m. 2H). 5.06(s. 1H). 5.39(s. 1H).
7.10-7.35(m. 10H). 8.67(t. J=5.7Hz. 1H).
10.43(br s. 1H)

MASS(m/z) : 334($M^+$). 167. 123

Elemental analysis: $C_{21}H_{27}N_2O \cdot HCl$

| | | | | |
|---|---|---|---|---|
| Calculated value: | C 71.24. | H 7.34. | N 7.55. | Cl 9.56 |
| Actual value: | C 71.30. | H 7.62. | N 7.52. | Cl 9.73 |

Example 33

A mixture of 2-chloro-2,2-diphenyl acetyl chloride (0.80 g) and 4-diethylaminomethylpiperidine (0.51 g) were stirred for a while at room temperature and diluted with methylene chloride (10 ml). The resulting mixture was stirred for 1 hour at the same temperature, and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with sodium hydroxide aqueous solution and water, dried over magnesium sulfate, and evaporated in vacuo. The residue was dissolved in dioxane (7.4 ml) and 1N hydrochloric acid (3.7 ml). The solution was stirred at 90 ℃ for 1 hour and 30 minutes, evaporated in vacuo, and extracted with ethyl acetate. The extract was washed with sodium hydroxide aqueous solution and water, dried over magnesium sulfate, evaporated in vacuo, and chromatographed over silica gel

using chloroform and methanol as an eluent to afford 1-(2,2-diphenyl-2-hydroxyacetyl)-4-diethylaminomethylpiperidine (0.33 g) as an oil, which was converted to the hydrochloride (0.20 g) in a usual manner.

free base:

NMR(CDCl$_3$, $\delta$) : 0.93(6H, t, J=7Hz, $CH_3 \times 2$),
0.95-1.95(5H, m, piperidine CH, $CHCH_3$),
2.06(2H, d, J=6.5Hz, $CHCH_2N$),
2.43(4H, quartet, J=7Hz, $N(CH_2CH_3)_2$),
2.68(2H, m, CONCH $\times$ 2), 3.59(1H, m, CONCH),
4.14(1H, m, CONCH), 6.22(1H, s, OH),
7.4(10H, m, aromatic H)

MASS(m/z) : 380($M^+$), 183, 86(base)

hydrochloride:

mp : 175-176 ℃ (recrystallization from isopropyl alcohol)

IR(Nujol) : 3400, 3160, 2760-2300, 1610$cm^{-1}$

NMR(DMSO-$d_6$, $\delta$) : 0.7(1H, m, piperidine CH),
1.05(1H, m, piperidine CH), 1.18(6H, t, J=7Hz, $CH_3 \times 2$)
1.45(1H, m, piperidine CH), 1.9(2H, m, piperidine CH),
2.65(2H, m, CONCH $\times$ 2), 2.8(2H, m, $CHCH_2N$),
3.05(4H, m, $N(CH_2CH_3)_2$), 4.15(1H, m, CONCH),
4.4(1H, m, CONCH), 5.92(1H, s, OH),
7.3(10H, m, aromatic H), 9.9(1H, br, HCl)

MASS(m/z) : 380($M^+$), 183, 86(base)

Elemental analysis: $C_{..}H_{..}N_2O_{..}\cdot HCl\cdot 1/2H_2O$

Calculated value: C 67.67, H 8.04, N 6.58, Cl 8.32

Actual value: C 67.62, H 8.08, N 6.51, Cl 8.32

Example 34

A solution of 4-bromo-2,2-diphenylbutanoic acid and thionyl chloride (1.37 g) in dry chloroform (20 ml) was refluxed for 4 hours and evaporated in vacuo to afford the corresponding acid chloride.

To a mixture of 4-aminomethyl-1-ethyl-1,2,3,6-tetrahydro-pyridine (0.73 g) and triethylamine (2.6 ml) in dichloromethane (15 ml) was added the obtained crude acid chloride in dichloromethane (15 ml) at room temperature and the resulting mixture was stirred overnight. The solvent was evaporated in vacuo, and ethyl acetate and 1N aqueous sodium hydroxide were added to the residue. The organic layer was separated, washed with water (three times) and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of dichloromethane and methanol (15:1) as an eluent, further on alumina with a mixture of n-hexane and ethylacetate (20:1) as an eluent. The obtained free base was treated with fumaric acid (229 mg) in a usual manner to give 1-[(1-ethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]-3,3-diphenyl-2-pyrrolidinone fumarate (0.54 g).

(

mp : 90℃ ~ (resolution) (washed with n-hexane)

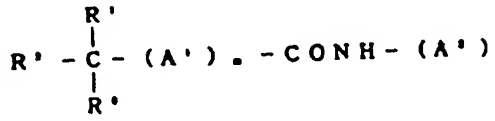
IR(Nujol) : 2500. 1680. 800. 770. 750. 700cm$^{-1}$

NMR(DMSOd$_6$. $\delta$) : 1.11(t. J=7.2Hz. 3H). 2.17(br s. 2H).
2.73(q. J=7.2Hz. 2H). 2.80-2.90(m. 4H). 3.24(br s. 2H)
3.86(s. 2H). 4.11(t. J=6.4Hz. 2H). 5.53(s. 1H).
6.52(s. 2H). 7.10-7.40(m. 10H)

MASS(m/z) : 360(M$^+$). 238. 165. 123

WHAT IS CLAIMED IS:

1. Substituted acetamide compound and a pharmaceutically acceptable salt thereof wherein the general formula is represented by the following formula (I):

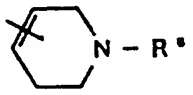


(I)

wherein $R^1$ and $R^2$ are each aryl which may have suitable substituent.

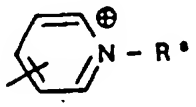
$R^3$ is hydrogen, hydroxy or lower alkyl.

$R^4$ is a group represented by the following formula (i), (ii), (iii) and (iv):



(i)

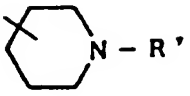
wherein $R^5$ is hydrogen, methyl, ethyl, propyl, isopropyl or imino protective group.



(ii)

wherein $R^6$ is lower alkyl.

(III)



(IV)

wherein $R^7$ is hydrogen, lower alkyl or imino protective group,

$A^1$ and $A^2$ are each lower alkylene, and

m and n are each 0 or 1, provided that

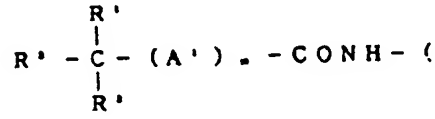
(a) $R^5$ is not ethyl when $R^1$ and $R^2$ are both phenyl, $R^3$ is hydroxy, $A^2$ is methylene, m is 0 and n is 1,

(b) $R^7$ is not methyl when $R^1$ and $R^2$ are both phenyl, and m and n are both 0.

2. Pharmaceutical preparation for prevention and/or treatment of dysuria comprising, as an active ingredient, substituted acetamide compound as defined in claim 1.

ABSTRACT

A compound having an anticholinergic activity represented by the following general formula (I):

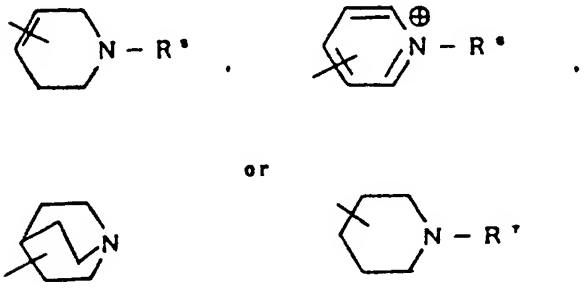


(I)

, wherein $R^1$ and $R^2$ are each aryl which may have suitable substituent,

$R^3$ is hydrogen, hydroxy or lower alkyl,

$R^4$ is a group represented by the following formula (i), (ii), (iii) or (iv):



$A^1$ and $A^2$ represent each lower alkylene, and m and n represent each 0 or 1.